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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,181	12/27/2005	Luigi Naldini	1130-PCT-US	1875

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,181	NALDINI ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/21/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/21/05,12/5/06,5/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Priority

Priority for the claimed invention is granted back to the filing date of the PCT/IT04/00227 application (04/21/2004). Specifically, the 60/456,080 application does not provide support for a "full efficient promoter" and no support for an efficient promoter from any animal gene. Also, no support can be found for a full efficient promoter consisting of a enhancer region and a second minimal promoter.

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Chtarto et al. (US 6,780,639, filed 8/24/2004).

Applicants claim a bidirectional promoter (in the context of a expression construct or gene transfer vector) for expression of at least two coding sequences in opposite direction in animal cells comprising 5' end to 3' end: a) a first minimal promoter sequence derived from cytomegalovirus (CMV) or mouse mammary tumor virus

(MMTV) genomes; b) a full efficient promoter sequence derived from an animal gene (can be phosphoglycerate kinase or ubiquitin); the two promoter sequences driving a coordinate transcription of said coding sequences in the opposite orientation, as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites, at least one IRES element, etc. Applicants also claim use of the construct for delivery and expression of multiple genes in animal (human) cells (can be neurons) wherein the cells can be *ex vivo*.

The examiner is interpreting the claim language as follows. Applicants recite promoter sequences "derived from" or "derives from" various sources such as CMV or MMTV or the phosphoglycerate kinase or ubiquitin genes). Applicants do not define the subjective terms "derived from" or "derives from" in the instant application and applicants do not disclose what methods are used in deriving one sequence from another. Therefore, said terms will be given their broadest reasonable interpretation. A promoter sequence is considered derived from an original sequence if it shares one nucleotide in common with the original sequence because the steps involved in the derivation can comprise an unlimited number of sequence deletions, insertions and/or substitutions in the original promoter sequence.

Also, applicants define a "full efficient promoter" as: "In the ambit of the instant invention a full efficient promoter sequence means a sequence driving an efficient transcription of primary transcript." (p. 4, instant specification).

Chtarto et al. (see whole document, particularly Fig. 6, columns 5-8, Example 3, Claims 1-13) teaches expression vectors (which can contain AAV or retroviral

sequences) comprising a bi-directional promoter comprising two minimal CMV promoters (mini CMV promoters) oriented in opposite directions as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites and at least one IRES element. Chtarto et al. also recite use of the construct for delivery and expression of multiple genes in re-transplantable animal (human) cells (can be neurons) wherein the cells can be *ex vivo*. The tet operator sequences present between the minimal CMV promoters act as an enhancer.

Given applicants' definition of the terms "derived from" and "full efficient promoter", the mini CMV promoter described by Chtarto et al. must be considered a "full efficient promoter sequence derived from an animal gene" as it is capable of driving an efficient transcription of a primary transcript and comprises at least one nucleotide from a animal gene promoter sequence. Chtarto et al. therefore teaches the claimed invention.

Claims 1-4, 6-11 and 13-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Itoh et al. (US 6,995,011, filed 7/3/2002).

Applicants' invention is as described above. In addition, applicants claim a method for generating a transgenic non human organism comprising the step of transforming appropriate cells with an expression construct comprising the above recited bidirectional cassette and retroviral sequences as well as a method for coordinate expression of two exogenous coding sequences in a re-transplantable human hematopoietic cell.

Itoh et al. (see whole document, particularly Figs. 2-6, columns 7, 13, 15-16) teaches retroviral expression vectors comprising a bi-directional promoter comprising two minimal CMV promoters (Tet responsive promoter) oriented in opposite directions as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites and at least one IRES element. Itoh et al. also recite use of the construct for delivery and expression of multiple genes in re-transplantable animal (human) cells (can be hematopoietic cells) wherein the cells can be *ex vivo*. Itoh et al. also teaches use of the expression vectors to generate transgenic animals by transforming appropriate cells with said expression vectors. Itoh et al. therefore teaches the claimed invention.

Claims 1-4, 7-8, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Fux et al.

Applicants' invention is as described above.

Fux et al. (cited by applicants, see whole article, particularly the paragraph bridging pp. 109-110, Table 1, Fig. 1, p. 114) teaches bidirectional expression cassette systems comprising a minimal CMV promoter and a promoter derived from an animal gene (can be a minimal promoter) and a method for expression of multiple genes in animal (can be human) cells. Fux et al. therefore teaches the claimed invention.

35 USC 103(a) Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chtarto et al. or Itoh et al., either in view of Hope et al. (US 6,136,597).

Applicants' invention is as described above. In addition, applicants recite that the expression construct comprises a post-transcriptional regulatory element positioned upstream to one or each of the polyA sites.

Chtarto et al. and Itoh et al. are applied as above. Neither teaches inclusion of a post-transcriptional regulatory element positioned upstream to one or each of the polyA sites.

Hope et al. (see whole document, particularly the Abstract, last paragraph in column 2, column 3, column 16) teaches that inclusion of a post-transcriptional element such as a WPRE can enhance expression of a transgene in a target cell.

The ordinary skilled artisan, seeking to increase expression of a transgene, in cells transduced with a bi-directional expression vector system would have been motivated to combine the teachings of Chtarto et al. or Itoh et al. on the generation of expression vectors with bi-directional promoters with the teachings of Hope et al. on inclusion of WPRE elements in expression systems because Hope et al. teaches that inclusion of post-transcriptional elements such as WPREs increases the expression of transgenes contained in the vectors. It would have been obvious for the ordinary skilled artisan to do this because of the expected beneficial effect of increasing expression of the transgene(s) contained in the expression vectors. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success inn practicing the claimed invention.

35 USC 112, 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is vague in the recitation of "...tissue animal cells are comprising brain neurons". The language in this claim is confusing and renders the metes and bounds of the claimed subject matter unclear.

Claim 13 is vague in the recitation of "...coordinate expression of two exogenous coding sequences into an animal cell...". It is unclear if applicants mean to introduce the sequences into the cell or express the sequences in an animal cell.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID GUZO
PRIMARY EXAMINER

David Guzo
November 10, 2007